UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

June 26, 2003

MEMORANDUM

Subject: Acute Toxicity Review for EPA Reg. No.: 464-TRI/ Ucarcide SB 130

DP Barcode: D290095

To: Marshall Swindell, PM 33 / Portia Jenkins
Regulatory Management Branch
Antimicrobials Division (7510C)

From: Ian Blackwell, Biologist
Efficacy Evaluation Team
Product Science Branch
Antimicrobials Division (7510C)

Through: Karen Hicks, Team Leader
Chemistry and Toxicology Team
Product Science Branch
Antimicrobials Division (7510C)

6/26/03

Michele E. Wingfield, Chief
Product Science Branch
Antimicrobials Division (7510C)

Applicant: The Dow Chemical Company

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Glutaraldehyde	30
Other Ingredient(s):	70
Total:	100%

I BACKGROUND: The Dow Chemical has submitted a set of twenty studies to support the registration of their product, Ucarcide SB 130 Antimicrobial. Although these studies were submitted for an acute toxicity / precautionary labeling review, not all of them are acute toxicity studies. The MRID Numbers are 459134-04, and, 459134-08 through 459134-27.

PSB/AD notes that while the registrant cites many studies for this submission, we do not know if the registrant has permission to cite these studies. PSB/AD requests that the PM Team determine if the registrant has made requests to pay for the data that they are citing to support this submission.

This submission includes the document "*Petition for Citation/Waiving the Requirements of the Six Acute Toxicological Studies for UCARCIDE™ SB 130 Antimicrobial*". This report was written by P.J. Spencer of the Toxicology & Environmental research and Consulting Laboratory of The Dow Chemical Company. This report does not have a report number and was not assigned an MRID Number. The following information is expressed in that report:

1 Acute oral toxicity:

A Acute oral toxicity studies carried out using various solutions of glutaraldehyde demonstrate a trend for enhanced toxicity as dilution increases while more concentrated solutions of glutaraldehyde are likely to produce severe gastrointestinal irritation.

B Products containing greater than 25% glutaraldehyde are classified as Tox Category II.

C This report presents a table wherein one 25% solution of glutaraldehyde has an acute oral LD_{50} of 385 mg/kg, and, a 45% solution of glutaraldehyde has an LD_{50} of 540 mg/kg.

2 Acute dermal toxicity:

A Data from dermal toxicity studies conducted with concentrations of 25-50% glutaraldehyde demonstrate that toxic and lethal levels of glutaraldehyde are capable of being absorbed through the skin of rabbits.

B A dose-response in lethality is apparent in that significantly less lethality is observed at concentrations of 25% glutaraldehyde as compared to the 50% concentration. Therefore, prolonged dermal contact with UCARCIDE SB 130 Antimicrobial, similar to the 25% aqueous solutions presented in Table 2 (see attached) can be

expected to result in adsorption of toxic, but less lethally toxic, levels than 50% glutaraldehyde solutions.

C Given that UCARCIDE SB 130 is a solid, absorption via the dermal route would be appreciably less on dry skin than that observed for aqueous glutaraldehyde solutions of similar concentrations.

D PSB/AD notes that for two of the studies tested on 25% glutaraldehyde, while the LD_{50} fell into toxicity category III, the statistical Confidence Intervals were 316-**8911** mg/kg, and, 266-**43,358** mg/kg.

E PSB/AD also notes that none of the identities of the test materials is reported. That is, while the percentage of glutaraldehyde in the test material may be 25 or 50%, the other 75-50% of the test material is not accounted for.

II RECOMMENDATIONS: PSB findings are:

1 MRID Number 459134-01: This is not an acute toxicity study, but is a particulate analysis of the (solid) product after it has been separated through a sieve. The results of this study are:

Table 1.

Particle Size	Percentage Range
≥ 2 mm	3.01- 4.08
≥ 1 mm	87.09 - 90.81
≥ 425 µm	98.49 - 99.39
≥150 µm	99.74 - 99.83
≥ 75 µm	99.87 - 99.91

This information appears to have been submitted in support of a waiver of the acute inhalation toxicity study. It may be used in conjunction with other studies included in this submission to support the request for a waiver of the acute inhalation toxicity study for 464-TRI.

2 MRID Number 459134-08: "Miscellaneous toxicity studies 25% Glutaraldehyde" by Maureen Miksztal. The Dow Chemical Company. Project Report: 39-40. Final Report Date: 4/11/2003. The report covers a study that was conducted in 1976 by the Carnegie-Mellon Institute of Research. It covers acute oral testing of 25% glutaraldehyde in water along with primary eye irritation studies conducted on totally different products. The acute oral LD_{50} was reported as 1.54 mL/kg → 1.052 g/kg.

A The report states that this study was not conducted in accordance with the GLP standards of the 40 CFR 160.
B The testing methods used in this study were vague and incomplete.
C The length of the study (the time the animals were allowed to be exposed to the test material before the study was concluded) was not reported.

3 MRID Number 459134-09: "Range Finding Tests on Glutaraldehyde, 45% Aqueous" by Maureen Miksztal. Mellon Institute. Project Report: 27-137. Final Report Date: 4/11/03. This report, like 459134-08, describes old acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, primary skin irritation and primary eye irritation studies. The study that is the basis of this report was conducted 9/30/64. This study was not conducted according to GLPs. This study reports the following:

A The acute oral toxicity study was conducted using three different dosages of 45% glutaraldehyde (2.0, 1.0 and 0.5 mL/kg). Please refer to the attached table (Table 27-551). The LD_{50} was determined to be 0.54 (0.38 to 0.76) g/kg.
B The acute dermal toxicity study was conducted using three different dosages of 45% glutaraldehyde solution. The three dosages tested were 1.0, 0.5 and 0.25 mL/kg. The LD_{50} was determined to be 250 mg/kg on the basis of the contained active ingredient. Please refer to table 27-552.
C The acute inhalation study was conducted using a concentration of 12.58 mg/L for 8 hours in a nine liter chamber. These testing methods do not meet current Agency standards. Also, this study does not report any mortality (no LC_{50} was reported), nor does it report the sexes of the animals.
D The primary eye irritation test was reported as causing severe necrosis after a 24-hour exposure to 0.005 mL of the 45% solution of glutaraldehyde.
E The primary skin irritation study used 0.01 mL of the 45% glutaraldehyde solution. This study was said to have caused "no discernible irritation". However, using current Agency guidelines, this study is to have used 0.5 mL of the test material. This study is unacceptable.

The acute toxicity profile from MRID Number 459134-09 is:

acute oral toxicity	II
acute dermal toxicity	II
acute inhalation toxicity	not determined
primary eye irritation	I

primary skin irritation	Unacceptable
dermal sensitization	Not conducted

(Note: This acute toxicity profile only pertains to MRID Number 459134-09 for a 45% glutaraldehyde product. It will be used to determine the profile for 464-TRI, but is not the profile of 464-TRI itself.)

4 MRID Number 459134-10: "*Miscellaneous Toxicity Tests Glutaraldehyde 25%*" by Roy C. Myers, Elton R. Homan, Charles Carpenter and Eugene Cox. Carnegie-Mellon Institute of Research. Project Report: 41-77. Study Date 5/1/78. This report, like 459134-08 and -09, describes old acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, primary skin irritation and primary eye irritation studies. This study that is the basis of this report was conducted 5/1/78. This study was not conducted according to GLPs. (It was conducted six years before the implementation of EPA's GLPs.) This report also accounts acute toxicity and irritation data on several chemicals other than glutaraldehyde (e.g., Simoniz Professional Cleaner/Wax, Tergitol HDL, and UCAR latex) that are not pertinent to this review of glutaraldehyde. This report gives the following information:

A Acute dermal toxicity study: Glutaraldehyde, 25% solution. LD_{50} = 16.0 (1.25-204) mL/kg → 10.928 g/kg.

5 MRID Number 459134-11: "UCARCIDE® Antimicrobial 130 LT: Acute Percutaneous Toxicity Testing Using the Rabbit" by R.C. Myers and S.M. Christopher. Bushy Run Research Center. Lab Project ID: 92U1064. Study Completion Date: 3/5/93. (This study was not reviewed for this submission.)

This acute dermal toxicity study was conducted using one of the products cited by the Dow Chemical Company, EPA Registration Number 464-714. This study reported an LD_{50} for males, females, and, for males and females.

males LD_{50} = 3.25 (2.40-4.39) g/kg	III
females LD_{50} = 3.25 (2.36-4.47) g/kg	III
combined LD_{50} = 3.25 (2.68-3.95) g/kg	III

6 MRID Number 459134-12: "Glutaraldehyde Six-Hour Static LT_{50} on Rats" by Donald J. Nachreiner, William M. Snellings and Fred. R. Frank. Project Report: 44-97. Report Date: 11/16/81. Final Report Date: 4/11/2003.

This "LT_{50}" study is an acute inhalation toxicity study that was conducted on Ucarcide Antimicrobial 250, a 50% glutaraldehyde product. This study was not conducted according to GLPs. (It was conducted almost three years before the implementation of EPA's GLPs.) This study was conducted as a six-hour exposure. The results of this study are that the LC_{50} of the 50% glutaraldehyde solution tested was over 0.19696 mg/L. This study did not determine or bracket the LC_{50} of this test material.

7 MRID Number 459134-13: "UCAR Tanning Agent G-51: Range Finding Toxicity Testing" by Roy C. Myers, Elton R. Homan, Carrol S. Weil and Fred R. Frank. Carnegie-Mellon Institute of Research. Project Report: 42-53. Report Date 5/21/79. Final Report Date: 4/11/03. This study will not be considered for this review of Ucarcide, as it was apparently conducted on a (leather?) tanning agent. It does not appear from the report to contain glutaraldehyde.

8 MRID Number 459134-14: "50% Glutaraldehyde Samples: Primary Dermal Irritancy in the Rabbit" by Kathleen R. Hufford, Mary G. Brawley and Nick S. Bellich. Project Report: 51-14. Report Date: 6/2/88.

This primary dermal irritation study was tested using several similar products. The report summarized the results of the study as follows:

A Ucarcide 250, 4 hour contact: moderate erythema on 6 of 6 rabbits, minor to severe edema on 6, necrosis on 6, desquamation on 5, alopecia on 2, scabs on 3 from 0.5 mL; no erythema or edema after 10 days. Corrosive by Department Of Transportation (DOT) definition.

B Ucarcide 250, 60 minute contact: minor to moderate erythema on 6 of 6 rabbits, no edema on any of 6, desquamation on 6, necrosis (not well-defined) on 1 from 0.5 mL; no erythema after 7 days.

C BASF 50% glutaraldehyde, 4 hr contact: moderate to severe erythema and edema on 6 of 6 rabbits, necrosis on 6, desquamation on 6, fissuring on 3, alopecia on 6, scabs on 6 from 0.5 mL; no erythema or edema after 10 days. Corrosive by DOT definition.

D BASF 50% glutaraldehyde, 60 min. contact: minor to moderate erythema on 6 of 6 rabbits, minor transient edema on 2, desquamation on 4, necrosis (focal or diffuse) on 3 from 0.5 mL; no erythema or edema after 7 days.

E BASF 50% glutaraldehyde, 3 minute contact: minor erythema on one rabbit, no edema on any of 6 from 0.5 mL; no irritation after one day.

9 MRID Number 459134-15: "50% Glutaraldehyde (Ucarcide 250): Primary Skin Irritancy Studies in the Rabbit" by Roy C. Meyers, Darol E. Dudd,

and Fred R. Frank. Bushy Run Research Center. Project Report: 52-116. Report Date: 1/9/90.

This primary skin irritation study was conducted using one-hour and three-minute exposure periods with a 0.5 mL dosage of the test material, Ucarcide 250. The "interpretation" of this study stated: "A one-hour application of UCARCIDE® 250 to covered rabbit skin resulted in severe irritation, including full-thickness necrosis on most rabbits. A 3-minute application of 0.5 mL produced only minor transient irritation on half of the animals tested. Therefore, UCARCIDE® 250 was 'corrosive' to the skin when tested for one hour but not in the 3-minute test."

10 MRID Number 459134-16: "Eccrine Anhidrosis Due to Glutaraldehyde, Formaldehyde and Iontophoresis" by B.I. Gordon, and Howard Maibach. The Journal of Investigative Dermatology. Vol. 53, No. 6. 1969. Anhidrosis is defined as "the normal deficiency of sweat". This study does not appear to pertain to this acute toxicity/ primary irritation review and was not reviewed for this submission.

11 MRID Number 459134-17: "Development and validation of an alternative dermal sensitization test: The mouse ear swelling test (MEST)" by Shayne C. Gad et al. Toxicology and Applied Pharmacology **84**, 93-114 (1986). This study was conducted as an assay of an alternative dermal sensitization test: The Mouse Ear Swelling Test (MEST). The study abstract states that this study correctly identified 71 of 72 materials tested as potential human sensitizers or nonsensitizers. Table 3 of this study lists glutaraldehyde as sensitizing 67% of the mice tested.

12 MRID Number 459134-18: "Contact Hypersensitivity Response to Glutaraldehyde in Guinea Pigs and Mice" by Malvin L. Stern et al. Toxicology and Industrial Health, Vol. 5, No. 1, 1989. The study conclusion was that both mice and guinea pigs demonstrated dose-dependent contact hypersensitivity responses to glutaraldehyde.

13 MRID Number 459134-19: "Examination of the Local Lymph Node Assay for Use in Contact Sensitization Risk Assessment" by G. Frank Berberick et al. Fundamental and Applied Toxicology, 19, 438-445 (1992). This study failed to demonstrate dermal sensitization to glutaraldehyde. There was no dpm-fold increase reported for glutaraldehyde in this study.

14 MRID Number 459134-20: "UCARCIDE 250 Antimicrobial: DOT Skin Corrosivity Test" by Roy C. Myers. Bushy Run Research Center. Project Report: 44-15. Report Date: 2/21/81. The study summary states that this material is a "corrosive" to the skin by DOT definition.

15 MRID Number 459134-21: "Total IgE Antibody Production in BALB/c Mice after Dermal Exposure to Chemicals" by David Potter and Karen S. Wederbrand. Fundamental and Applied Toxicology, 26, 127-135 (1995). When diluted in a 50:50 acetone and water solution, a significantly higher IgE response was demonstrated than what was obtained from control animals.

16 MRID Number 459134-22: "The Use of Graded Concentrations in Studying Skin Sensitizers: Experimental Contact Sensitization in Man" by F.N. Marzulli. Fd Cosmet. Toxicol., Vol. 12, pp. 219-227. Pergamon Press, 1974. (Great Britain). This particular study demonstrated a 0/102 sensitization response when using the Draize assay. However, the article went on to state that it is often claimed that "the Draize test is of little value."

17 MRID Number 459134-23: "*The* Dose Response Relationships in Allergic Contact Dermatitis: Glutaraldehyde-containing Liquid fabric softener" by James E. Weaver and Howard I. Maibach. Contact Dermatitis, 1977, Vol. **3**, 65-68. When exposed to a formulation containing **550 ppm glutaraldehyde**, dermal sensitization was not elicited in challenge tests of 16 GTA-sensitive subjects, or, in repeated insult patch tests of 706 normal human male and female subjects. PSB/AD notes that this study intentionally used an extremely dilute dosage of glutaraldehyde. This test of a 550 ppm dilution of glutaraldehyde will have little relevance to the dermal sensitization potential of the 30% glutaraldehyde registration product when one takes the other dermal sensitization data presented (e.g., MRID Numbers 459134-17 and -18) for this submission into consideration.

18 MRID Number 459134-24: "Dermal Sensitizing Potential of Glutaraldehyde: A Review and Recent Observations" by Byan Ballantyne, M.D., and, Brian Berman, M.D. J. Toxicol. – Cut. & Ocular Toxicol., 3(3), 251-262 (1984). The conclusion of this paper states: "**Glutaraldehyde has the potential to cause a low incidence of dermal hypersensitization reactions, with an eliciting threshold concentration of 0.5% in water. Cross reactivity to formaldehyde does not occur.**"

19 MRID Number 45914-25: "A Screening Assessment of Potential Inhalation Exposure to Glutaraldehyde from Use of Ucarcide™ SB 130 Antimicrobial" by James R. Weldy. Final Report Date: 4/7/2003.

Waiver candidates based on volatility may include, but not be limited to: viscous liquids (under conditions of use), waxes, resins, lotions and caulks. This study (page 6 of 12) states: "Glutaraldehyde is released at

a relatively slow rate from the silica consistent with its low vapor pressure (0.33 mmHg at 20°C)[1], so additional volatilization of glutaraldehyde off of the silica carrier is unlikely to lead to significant exposures during brief pouring operations." EPA/OPP waivers are considered that have vapor pressures less than 7.5×10^{-5} mmHg (for products to be used indoors), and, less than 1×10^{-4} (for products to be used outdoors) at 20-30°C. **The cited vapor pressure of 0.33 mmHg at 20°C is far above both of the EPA/OPP limits.**

20 MRID Number 459134-26: "UCARCIDE™ SB 130 Antimicrobial: Resistance to Attrition" by J.A. Hotchkiss. Toxicology & Environmental Research and Consulting, The Dow Chemical Company. Lab Project Study ID: 031017. Study Completion Date: 4/44/2003. This report covers an attrition study on the test material. In one study the product was shaken over sieves of various sizes (see Table 2 below). In the other study, the test material was combined with steel balls in a sieve-bottom receiver pan for ten minutes. This study was conducted in accordance with the American Society of Testing Materials (ASTM) Test Method E728-91 – Standard Test Method for Resistance to Attrition of Granular Carriers and Granular Pesticides. Test Method E728-91 is the current EPA/OPP standard for the testing of resistance to attrition for the waiver of acute inhalation toxicity studies. When such a waiver is granted, a default toxicity category of IV is assigned.

Table 2. Particle Distribution of Lot # 0324-1 Ucarcide SB 130 After Shipping

Sieve Screen Size (Particles ≥ Screen Size Retained)	Percent of Sample Retained by Sieve
500 µm	95.4%
300 µm	3.5%
125 µm	0.9%
<125 µm	0.2%

Table 3. Resistance to Attrition of Ucarcide SB 130 After a Ten-Minute Exposure to 10-5/8 Inch Steel Balls Over a 38 µm Screen.

Sample No.	Test Sample Weight	Mass Recovered After Mechanical Abrasion (b)	Mass of Sample Retained by 125 µm Limit Screen (a)	Resistance to Attrition (a × 100)/b

1	50.0 g	48.2 g	34.1 g	70.7%
2	50.1 g	48.9 g	36.1 g	73.8%
3	50.1 g	49.0 g	34.2 g	69.8%
Resistance to Attrition = 71.4% ± 2.1% (mean ± Standard Deviation; n =3)				

These data demonstrate that this product is resistant to attrition, and is not likely to form respirable particles after shipping or mechanical abrasion.

21 MRID Number 459134-27: "Personal Short-Term Air Monitoring for Glutaraldehyde during Packaging of UCARCIDE SB 130" by James R. Weldy. The Dow Chemical Company. Final Report Date: 2/19/2003.

This study does not support a waiver of the acute inhalation toxicity study for this product. This report discusses the ACGIH TLV-Ceiling for glutaraldehyde. The EPA/OPP does not make regulation decisions based upon American Conference of Governmental Industrial Hygienists.

22 MRID Number 00060275: "Range Finding Tests on Glutaraldehyde, 45% Aqueous (Pentanedial, 45%)" by Jean A. Striegel. Report Number: 27-137. Report Date: 10/5/1964. This study is a range-finding study that covers the following areas of acute toxicity:

A Acute oral toxicity (Stomach Intubation) in the rat: LD_{50} = 1.30 mL/kg → 0.8879 g/mL.
B Acute dermal toxicity (skin penetration): LD_{50} = 2.54 mL/kg → 1.73 g/mL.
C Acute inhalation toxicity: "Substantially saturated vapor, static conditions at 20°C. 8 hours killed 0 of 6." This study did not assess the vapor concentration, the particle concentration, or, conduct a particle size determination.
D Primary eye irritation: Severe corneal injury, iritis, swollen and necrosed eyelids from 0.005 mL undiluted per eye, and from 0.5 mL per eye of a 5% dilution in distilled water.
E Primary skin irritation: 2 of 6 rabbits with necrosis. Corrosive.

23 MRID Number 164459: "Glutaraldehyde Dilutions, Percutaneous Toxicity and Eye Irritation Studies" by Brian Ballantine. Bushy Run Research Center. Project Report: 44-65. Report Date: 6/1/81.

A Percutaneous application, 50% glutaraldehyde solution: LD_{50} = 1.59 (0.701-3.59) mL/kg → 1.086 g/kg.

B Percutaneous application, 25% glutaraldehyde solution: LD_{50} = 8.00 mL/kg → 5.464 g/kg
C Percutaneous application, 5% glutaraldehyde solution: LD_{50} > 16.00 mL/kg → > 10.928 g/kg
D Eye irritation, 0.1 mL of **0.5**% solution: Only very slight conjunctival irritation was observed.

24 The acute oral toxicity cannot be bridged with the data presented in this submission. The theory is that a 30% solution of glutaraldehyde in water will be more readily absorbed than will a 30% dilution of glutaraldehyde in silica. While water is, of course, readily absorbed into the gut, silica is not. Thus, it is very possible that *what is absorbed into the gut* from a 30% glutaraldehyde in silica dilution will be more concentrated than a total 30% glutaraldehyde in water dilution. Also, the silica could cause an intestinal blockage, which would lead to problems physiological problems alone.

Most of the studies submitted for this review do not meet the Agency requirements for acute toxicity / primary irritation studies by themselves and would not be sufficient for determining acute toxicity categories. However PSB/AD is making an exception and accepting the submitted data as a whole for the following reasons:

A Acute dermal toxicity: The registrant submitted at least **six** acute dermal toxicity studies to support the categorization of this product. In these studies, the LD_{50}s were in the same toxicity category for the same, or similar, concentrations.
B Acute inhalation toxicity: The waiver criteria submitted for the acute inhalation toxicity study were not all acceptable. However, the registrant did meet the guidelines for a waiver of an acute inhalation toxicity study based upon attrition/ and particle size (the particles were too large).
C Primary eye irritation: Two of the primary eye irritation studies submitted found this active ingredient to be corrosive and necrotic (acute toxicity category I) to eyes at the test concentration of 45%. It is felt that reducing the concentration of active to 30% and adding an abrasive material (this product contains approximately 70% silica) will not change the toxicity category I assignment of this product.
D Primary skin irritation: Three primary skin irritation studies submitted to support this product found this product to be corrosive. They were conducted using 45% and 50% concentrations.
E This active ingredient was found to be a dermal sensitizer in three studies. This is considered by PSB/AD to be self-validation.

The acute toxicity profile for File Symbol 464-TRI is currently:

acute oral toxicity		Data requested
acute dermal toxicity	III	Cited
acute inhalation toxicity	IV	Waived
primary eye irritation	I	Cited
primary skin irritation	I	Cited
dermal sensitization	Sensitizer	Cited

III LABELING:

Currently, PSB/AD does not have enough information to recommend a complete set of precautionary labeling statements for this product. In order to have complete precautionary statements prescribed for this product, the registrant will have to fulfill the requirements for the acute oral toxicity study for 464-TRI.